

## CLINICAL REPORT

# Prostacyclin Reduces Symptoms and Sympathetic Dysfunction in Erythromelalgia in a Double-blind Randomized Pilot Study

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**Sympathetic dysfunction and skin microvascular arteriovenous shunting with insufficient nutritive perfusion and tissue hypoxia have been reported in patients with erythromelalgia. The objective of this study was to determine whether iloprost, a synthetic prostacyclin analogue – primarily a vasodilator and inhibitor of platelet activation – improves symptoms and sympathetic function in patients with erythromelalgia. Erythromelalgia is a rare condition, but we managed to collect 12 primary cases for a double-blind, randomized, parallel-group pilot trial evaluating the effect of iloprost ( $n=8$ ) and placebo ( $n=4$ ). The treatment effect was determined by the need for cooling of affected skin and by vasoconstrictor tests following Valsalva's manoeuvre and contralateral cooling. The results show a significant reduction in symptoms ( $p<0.05$ ) and sympathetic dysfunction ( $p<0.05$ ) in the iloprost group. Further studies with oral prostacyclins or analogues are suggested. Key words: clinical trial; erythromelalgia; iloprost.**

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Erythromelalgia (EM) is a rare disorder of skin circulation in the hands and/or feet. It is characterized by burning pain that is aggravated by warming and relieved by cooling, erythema and increased temperature of affected skin (1, 2). The condition can be primary or secondary to another disease (3).

The pathogenesis of EM is debated. Our group has previously hypothesized that EM is not a specific disease entity, but a symptom complex caused by one common pathophysiological mechanism: skin microvascular arteriovenous shunting with insufficient nutritive perfusion and a corresponding tissue hypoxia (4–6). Autonomic dysfunction (7–9) and endothelial injury (10) have also been reported, but it is not known whether these mechanisms are primary or secondary to the vascular dysfunction.

Reviews of current therapeutic approaches have been published recently (11–13), but the results have

generally been disappointing; no treatment apart from cooling is consistently effective, and the level of evidence behind each therapeutic approach is weak. Effects of parenteral prostaglandin E<sub>1</sub>, prostacyclins or prostacyclin analogues have been reported (4, 14). The theoretical rationale for these drugs is a dilatory effect on cutaneous circulation, cytoprotective and thrombocyte aggregation inhibitory effect (15–17). Our group has repeatedly argued that a maldistribution of skin microcirculation, with increased thermoregulatory shunt flow and an inadequate nutritional perfusion, is a pathomechanism in EM (4–6).

Our prestudy hypothesis was that the vasodilatory and thrombocyte aggregation inhibition effect of prostacyclin may improve nutritive perfusion. So far, no properly designed trial of drug treatment of EM has been published. Using both clinical and physiological endpoints, in this pilot study we report the results of a double-blinded, placebo-controlled, randomized trial of iloprost treatment in 12 patients with EM.

## MATERIALS AND METHODS

### Patients

From our database of patients with EM, 14 patients were recruited (18) and screened for laboratory abnormalities and current EM symptoms. Fertile females were instructed to practice medically approved contraception during the study. Exclusion criteria included confounding concurrent diseases or drugs, active gastrointestinal ulcerations, history of intracranial bleeding, pregnancy (positive gravitest) and deficient haemostatic function. Twelve patients [female/male=8/4, 52 (17–74) years (median with range), duration of EM 9.9 (3.6–23.4) years] were eligible for the study, with a definite diagnosis of primary EM localized to the feet. Informed written consent was obtained as well as approval from the local ethics committee and the Norwegian Medicines Control Board.

### Treatment and evaluation procedures

A double-blind parallel group trial was designed. The eligible patients were allocated to either iloprost ( $n=8$ ) or placebo ( $n=4$ ) infusions according to a weighted randomization schedule (Table I). A study nurse administered and monitored the treatment. Iloprost was diluted to a concentration of 0.2 µg/ml in saline identical in appearance to placebo (0.9% NaCl). The study medication was given in a peripheral vein for 6 h on 3 consecutive days while patients were hospitalized. The dosage was from 10 to 40 ml/h: On the first day of

Table I. Demographic and clinical characteristics of the patients with erythromelalgia (EM) allocated to either iloprost or placebo treatment (median with total range)

	Iloprost	Placebo	P
Female/male (n)	6/2	2/2	ns
Age (years)	39.0 (17.0–60.0)	56.0 (50.0–74.0)	ns
Duration of EM (years)	10.5 (5.7–14.9)	8.9 (3.6–23.4)	ns
Cooling score <sup>a</sup>	2.8 (1.9–4.0)	1.8 (0.4–3.6)	ns

<sup>a</sup>EM severity based on average need for cooling for one week prior to inclusion rated on an 8-point Likert (ordinal) scale: 1=no cooling and 8=continuous need for cooling or plexus/epidural anaesthesia.

treatment an infusion rate of 10 ml/h was given for 30 min, and then increased to 20 ml/h. The infusion rate on the second day started at 10 ml/h and titrated in increments of 10 ml/h at 30 min intervals up to a maximum of 40 ml/h, if tolerated. The tolerated infusion rate determined at day 2 was infused on day 3 for the whole 6-h treatment period unless side effects supervened. Disease severity was rated on an 8-point Likert (ordinal) scale (18). The score of 1 implies uncomfortably warm without the need for cooling of affected skin, while score 8 implies very strong burning pain with continuous need for cooling or plexus/epidural anaesthesia. This cooling score was determined by the patients at baseline and daily for the first week after treatment. The given values are weekly averages of the patients' daily assessments. Secondary outcome measures included tests of sympathetic function, where perfusion responses to Valsalva's manoeuvre (a deep breath and then forced exhalation for 15 s against a closed glottis) and contralateral cooling (contralateral foot into a water bath with temperature 15°C) were recorded. Vasoconstriction in response to these two manoeuvres is dependent on intact sympathetic function, and attenuation of vasoconstriction has been demonstrated previously in EM patients (9). The Laser Doppler flowmetry technique was used to quantify the skin microcircular perfusion in the affected skin of the pulp of the first toe. Perfusion tests were performed one month prior to and one month after therapy.

Safety monitoring included clinical examination and vital signs (baseline, during treatment and at follow-up visits), laboratory evaluations (one day before the start of therapy and before the third day of therapy), and recording of adverse events and an assessment made of their relationship to treatment (during treatment and follow-up visits). Laboratory evaluation included haematology, liver and renal function tests, glucose, electrolytes and urine stix.

The cooling score was analysed as continuous data. The data were skewed and therefore the Wilcoxon signed-ranks

test was used to analyse post-treatment as compared to pretreatment endpoints. Chi square and Mann-Whitney tests were used to compare discrete data. Significance levels are reported two-tailed and considered to be significant with  $P \leq 0.05$  using SPSS 10.0 software (SPSS Inc., Chicago, Ill., USA).

## RESULTS

The cooling score was significantly reduced in the iloprost group after treatment ( $P < 0.05$ ) as compared to baseline values (Table II). The reductions in flux after Valsalva's manoeuvre and contralateral cooling were significantly higher ( $P < 0.05$ ) one month after treatment with iloprost compared to the baseline values (Table II). No differences were demonstrated for the clinical and demographic data (Table I), nor for the primary and secondary endpoints (Table II) between the iloprost and placebo groups.

Mild adverse events were only reported among patients in the iloprost group: erythema ( $n=5$ ) or warm sensation ( $n=2$ ) at the injection site, headache ( $n=5$ ), nausea ( $n=1$ ) and hypotension ( $n=1$ ). The symptoms were dose-related and resolved rapidly on reduction of the infusion rate. Maximum dosage was tolerated for three patients in the iloprost group at the third day of intervention. No clinically significant changes in blood tests were demonstrated.

## DISCUSSION

This pilot study indicates that treatment with iloprost significantly reduces the need for cooling of the affected skin, and the sympathetic dysfunction, previously demonstrated in patients with EM, improves significantly.

EM is a rare condition. A limitation of this study was the low number of patients included. Previously, only case reports or small series with treatment of EM have been published. We managed to collect 12 patients – too small a number of patients to perform prestudy estimates of sample size based on power considerations. A weighted randomization was applied to get more patients in the iloprost group to make statistical analyses possible.

Relief by cooling of affected skin is the focus of

Table II. Effect of treatment on clinical and physiological outcome measures in patients with erythromelalgia (EM) (median with total range)

	Iloprost (n=8)		Placebo (n=4)	
	Pretreatment	After treatment	Pretreatment	After treatment
Cooling score (1–8) <sup>a</sup>	2.8 (1.9–4.0)	1.9 (0.1–3.0)*	1.8 (0.4–3.6)	1.2 (0.0–2.4)
Valsalva's manoeuvre <sup>b</sup>	44.1 (0.0–63.6)	64.2 (20.8–80.0)*	35.0 (0.0–66.7)	68.1 (0.0–80.0)
Contralateral cooling test <sup>b</sup>	32.9 (0.0–54.6)	67.9 (35.7–86.4)*	43.3 (0.0–79.0)	64.6 (30.0–88.2)

<sup>a</sup>EM severity based on average cooling score for one week rated on an 8-point Likert (ordinal) scale, 1=no cooling and 8=continuous need for cooling or plexus/epidural anaesthesia.

<sup>b</sup>Percentage reduction in flux after stimulus assessed by Laser Doppler flowmetry, median with total range.

\* $P < 0.05$  as compared to pretreatment values.

attention for patients with EM and their daily activities are often limited because of the need for cooling. Cooling score has previously been applied as an indicator of EM severity (18). Significant improvement in cooling score was observed in the iloprost group. Variability in EM symptoms is well known. Using mean values of daily recordings for one week reduced the effect of daily variations in symptoms. Two of the four placebo-treated patients also experienced a reduced need for cooling.

The physiological outcome measures were chosen based on the previous demonstration of attenuated vasoconstrictor responses involving central sympathetic reflexes in patients with EM (9). Also these physiological endpoints imply a positive treatment effect of iloprost with reversal of sympathetic dysfunction.

Deranged prostaglandin metabolism in relation to skin vasculature has been described in patients with EM (19). According to the microvascular shunt hypothesis of pathogenesis, vasoconstrictor treatment is contraindicated, while vasodilators such as sodium nitroprusside, prostaglandins and prostacyclins may enhance nutritional blood flow, improve tissue oxygenation and induce symptom relief (20). The dosage of iloprost was based on a previous study protocol, and before this study we had treated four patients with EM with beneficial effect using the same regimen (21). No dose-response study has been performed for the treatment of EM. The reported adverse events related to iloprost treatment may have confounded the blinding in this study.

The results of this study indicate that iloprost has a treatment effect on EM. Prostacyclin analogues are now commercially available as tablets, and we believe that the results of this pilot study give a rational basis for planning a properly designed placebo-controlled study of the effect of these analogues on a larger EM patient material.

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